REMARKS

Amendments In the Claims

Following amendment as requested herein, the following claims are pending in the present application: Claims 2–7, 9 and 16–20. Claims 1, 8 and 10–15 were previously canceled.

Claims 5 and 9 are amended to recite with further improved clarity that rotigotine is present in the composition in a concentration sufficient to provide a rotigotine flux that is therapeutically effective for treatment of Parkinson's disease. Previously the treatment of Parkinson's disease was recited only in the preamble of Claims 5 and 9, and by reciting it now in the body of each claim, there can now be no doubt that it gives life and meaning to the claim. The amendment also provides a functional definition of the concentration of rotigotine in the composition, namely one providing a therapeutically effective rotigotine flux for treatment of Parkinson's disease. This functional description of rotigotine concentration finds support in the specification as filed at least at p. 7, 5th paragraph.

Claim 9 is further amended to recite that the chloride salt is "pharmaceutically acceptable". Support for this amendment is found in the specification as filed, at least at p. 7, 6th paragraph.

While amending Claims 5 and 9, opportunity has been taken to delete redundant occurrences of the word "the" where antecedent basis is not required.

No new matter is introduced and no change in inventorship arises from any amendment made herein.

RESPONSE TO OFFICE ACTION DATED FEBRUARY 19, 2009

1. General Remarks

Applicant appreciates the Examiner's courtesy in calling counsel prior to issuance of the present Action to propose allowable subject matter. Unfortunately, the Examiner's proposal was in Applicant's view unnecessarily restrictive. Applicant prefers to continue prosecution via the present RCE.

2. Rejection Under 35 U.S.C. §103(a)

Claims 2–7, 9 and 16–20 stand rejected under 35 U.S.C. §103(a) as allegedly unpatentable over U.S. Patent No. 6,884,434 ("Müller") in view of Panchagnula *et al.* (2000)

Curr. Opin. Chem. Biol. 4:468–473 ("Panchagnula") and U.S. Patent No. 6,416,503 ("Suzuki"). This rejection is respectfully traversed.

2.1. The cited documents fail to teach or suggest all claimed features.

Even if motivation existed to combine Müller, Panchagnula and Suzuki, which is not admitted herein (see Applicant's response dated March 14, 2008), the cited combination fails to establish a *prima facie* case of obviousness, as the combination does not disclose all claimed features of the instant claims. A *prima facie* case of obviousness requires that the combined references teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Or, if the references-in-combination are missing claimed features, there must be some apparent reason either in the references or the general knowledge in the art to modify the references to include the missing subject matter. MPEP 2144.I.

2.1.1. Treatment of Parkinson's Disease By Application of an Iontophoretic Device

Independent Claims 5 and 9 are directed to a method for treatment of Parkinson's disease by applying an iontophoretic device comprising a rotigotine-containing composition. As admitted in the present Action (p.4), Müller "does not teach treating Parkinson's disease transdermally by application of an iontophoretic device." The missing element of treatment of Parkinson's disease by iontophoresis is not supplied by Panchagnula or Suzuki. Thus, even if, *arguendo,* motivation existed to combine Müller, Panchagnula and Suzuki, an essential claim element, namely treating Parkinson's disease by application of an iontophoretic device, is not taught or suggested by the combination.

Neither the documents themselves nor general knowledge in the art offers a reason to modify the cited documents in a way that would lead to the method of Claims 5 or 9, *i.e.*, a method for treating Parkinson's disease by iontophoresis. Indeed, the art discourages one of ordinary skill in the art from attempting such a method. For example, as indicated in the present specification as filed (passage bridging pp. 4–5 and art cited therein), approaches to develop a system for iontophoretic administration of apomorphine and ropinirole have been unsuccessful in generating sufficient flux to achieve plasma concentrations above a minimum for therapeutic efficacy.

Further, the transdermal therapeutic system of Müller relies on the fact that release of

rotigotine free base is markedly improved as compared to the use of salts (Müller, col. 5, lines 7–14). Thus, in reading the Müller disclosure as a whole as required under MPEP 2141.02.VI, Müller can be seen to teach away from use of electrolytes, which is a requirement for drug delivery by iontophoresis.

Still further, as stated by Panchagnula (abstract), iontophoresis is primarily used for delivery of large and charged molecules. Because rotigotine free base as delivered by Müller is not a large and charged molecule, one of ordinary skill would be further discouraged by Panchagnula in attempting iontophoresis for delivery of rotigotine, or for treatment of Parkinson's disease thereby.

By failure of the cited combination of documents to teach or suggest a method of treating Parkinson's disease by application of an iontophoretic device, and by the demotivating disclosure of such reference-combination to the skilled person who might otherwise contemplate such a method, a *prima facie* case of obviousness of Claims 5 or 9 cannot be sustained.

2.1.2. Triethylammonium Chloride and Tributylammonium Chloride

Independent Claim 5 is directed to a method wherein the iontophoretic device applied comprises a composition containing, in addition to rotigotine, "at least one chloride salt selected from the group consisting of triethylammonium chloride, tributylammonium chloride and combinations thereof." The Action acknowledges that none of the cited references discloses any of these chloride salts, but at p. 3 asserts that "[b]y Applicant's own admission in the specification in the last paragraph on page 7 spanning into page 8, all chloride salts which are pharmaceutically acceptable may be employed in the composition of the invention" and that "[i]t is also taught that NaCl, triethylammonium chloride and tributylammonium chloride are art equivalent as being used in the invention."

As articulated in Applicant's response submitted on September 22, 2008 (see pp. 4–6 thereof), Applicant has made no admission as to equivalence of triethylammonium chloride (TEACl) and tributylammonium chloride (TBACl) to NaCl. Examples 2 and 3 of the specification as filed highlight that NaCl, TEACl and TBACl are not bioequivalent. Indeed, the paragraph bridging pp. 7–8 cited in the Action explicitly sets forth that TEACl and TBACl

are preferred over NaCl because they result in higher fluxes of rotigotine. Thus, although any pharmaceutically acceptable chloride salt can be used, all such salts are not equivalent to one another.

Furthermore, as previously pointed out, the obviousness-rejection is based upon impermissible hindsight inasmuch as the "art equivalence" alleged (incorrectly) is entirely and admittedly predicated on disclosure in Applicant's specification. An obviousness inquiry cannot include knowledge gleaned only from Applicant's disclosure. MPEP 2145.X.A, citing *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Prior to the present invention, there was no apparent reason for a skilled artisan to select TEACl and/or TBACl in place of NaCl. The combination of Müller, Panchagnula and Suzuki fails to teach or suggest the particular chloride salts recited in Claim 5, and further fails to appreciate any benefit, advantage or even suitability of including these particular chloride salts. And no reason based on general knowledge in the art has been articulated in the Office Action to insert the missing subject matter. In view of these deficiencies in the Action, a *prima facie* case of obviousness of Claim 5 cannot be sustained.

2.2. Predictability necessary for a showing of obviousness is missing.

The Examiner appears to be applying the "obvious to try" standard in making the present rejection. This standard has been sanctioned by the U.S. Supreme Court in *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) but with the proviso that there has to be "a finite number of identified, predictable solutions" (emphasis added). Furthermore, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *Id.* (emphasis added). In paraphrasing *KSR*, MPEP 2143.01.III states that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art" (emphasis in original).

Applicant submits that the person of ordinary skill in the art at the time of the present invention could not have predicted that iontophoresis of rotigotine according to the present method would be successful in providing sufficient flux for therapeutic efficacy in treating Parkinson's disease. In other words, at the time of the present invention there was no

reasonable expectation of success.

2.2.1. Effect of chloride salt on rotigotine flux does not lead to predictable success.

As stated in the present specification (p. 7, 4th paragraph), to provide optimal flux of rotigotine across human stratum corneum, it was determined by the present inventors that a sufficient amount of Cl^- ions was necessary. The Action asserts that one would have been motivated by Suzuki "to add sodium chloride in an effort to further improve drug delivery." Even if, *arguendo*, Suzuki provides such motivation, the resultant combination is not obvious "unless the results would have been predictable to one of ordinary skill in the art" (MPEP 2143.01.III, citing *KSR, supra*). That predictability is missing here.

First, as taught in the present specification (p. 7, 4th paragraph), "addition of chloride salts reduces the solubility of rotigotine." One of ordinary skill in the art observing this reduction in solubility would be led to expect low flux of rotigotine in presence of NaCl. Indeed, the publication of Nugroho, *et. al.* (2005) Transdermal Iontophoretic Delivery of Dopamine Agonists: *In Vitro–In Vivo* Correlation Based on Novel Compartmental Modeling (Doctoral thesis, Leiden University), Chapter 3, pp. 37–53 (cited in the IDS submitted herewith), confirms that when NaCl concentration is increased from 0.07M to 0.14M (70 to 140 mmol/l), a substantial reduction in flux results. Thus, if any predictability were present with regard to effect of chloride salts on rotigotine flux, it is predictability not of success, but of failure. It certainly was unpredictable that in presence of 1–140 mmol/l chloride salt, rotigotine would exhibit sufficient flux to provide a therapeutically effective plasma concentration.

2.2.2. Cited documents provide evidence of unpredictability.

Panchagnula summarizes the hope and potential surrounding iontophoresis, but, as admitted in the Action (p. 2), includes several remarks on limitations and practical considerations that must be accounted for when using the technique. It appears, however, that no weight has been given to Applicant's evidence in this regard, as contained in the responses submitted on September 22, 2008 and March 14, 2008. Therefore, the evidence of unpredictability as set forth by Panchagnula is presented once again for the Examiner's full consideration.

Panchagnula states that skin is a complex membrane that has great influence on the movement of molecules across it in the presence of an electric field, which has posed an obstacle to determination of an exact relationship for iontophoretic transport (page 468, col. 2). In addition, Panchagnula illustrates that iontophoresis requires investigation on a case-by-case basis, meaning that one set of conditions cannot reasonably be expected to work for different molecules. To wit:

- "[C]hanges in skin charge distribution as a function of the physico-chemical properties of the permeant in realistic formulation conditions remains to be explored" (page 469, col. 1).
- "[E]xtensive studies need to be done with a series of small molecules and macromolecules to understand the exact role of the physico-chemical properties of penetrant in relation to iontophoretic delivery" (page 469, col. 2).
- "One of the main issues with regard to the formulation is ensuring the stability of the drug under the influence of an electric field and, until now, only a few studies have been carried out on this aspect" (page 472, col. 1).
- Iontophoresis "will have to overcome much tougher obstacles than its passive counterparts before it can make a lasting impact in the years to come" (page 472, col.2).

It is clear from Panchagnula that iontophoresis is not a "turn-key" delivery system, and that a drug cannot be simply added to a predefined system with any reasonable expectation or predictability of success. Accordingly, as evidenced by Panchagnula, there is no "finite number of identified, predictable solutions" per *KSR*; thus the method of Claims 5 and 9 would not have been predictable to one of ordinary skill in the art. For this reason, as well as for other reasons set forth above, a *prima facie* case of obviousness cannot be sustained against Claims 5 and 9.

Each of Claims 2–4, 6, 7 and 16–20 depends from and incorporates all limitations of either Claim 5 or Claim 9 and is therefore non-obvious for at least the same reasons that Claims 5 and 9 are non-obvious.

2.3. Rebuttal Evidence: Failure of Others

Even if a *prima facie* case of obviousness could be plausible posed (which is not admitted herein), any such case is overcome by evidence of the failure of others. See *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) as further sanctioned by *KSR, supra* ("the [*Graham*] factors continue to define the inquiry that controls").

As articulated above, as detailed in previous responses, and as recited in Applicant's specification, others have failed in attempts to develop adequate iontophoretic systems for delivery of anti-Parkinson's disease drugs. For example, attempts to deliver apomorphine and ropinirole hydrochloride have resulted in minimally effective therapeutic levels of the drug in plasma (see specification as filed at pp. 4–5). By now providing a method by which the anti-Parkinson's disease drug rotigotine can be successfully delivered iontophoretically, the present inventors have succeeded where others have failed.

Applicant respectfully submits that this success in view of others' failure to provide an iontophoretic treatment for Parkinson's disease is sufficient evidence of non-obviousness to overcome any *prima facie* obviousness (which, as shown above, is not in any case sustainable).

2.4. Rejection Under 35 U.S.C. §103(a): Conclusion

As detailed above, the instant claims are not obvious over the cited combination of documents, at least because:

(1) the cited documents do not teach or suggest all the claim limitations;

(2) there is no reason in the cited documents or general knowledge in the art to modify the references to include the missing claim limitation;

(3) the predictability of success needed for a showing of *prima facie* obviousness does not exist; and/or

(4) failure of others to provide a successful iontophoretic treatment for Parkinson's disease is sufficient to overcome any *prima facie* case of obviousness that could be made.

Applicant respectfully requests withdrawal of the present rejection under 35 U.S.C. §103(a) over Müller in view of Panchagnula and Suzuki.

3. Examiner's Comment Re "commensurate in scope"

Although no rejection is made on this ground, Applicant responds to the comment in the Action (p. 3) that Claims 5 and 9 are allegedly "not commensurate in scope with the claimed invention because any dose of rotigotine is contemplated with no supporting data with a wide range of doses." Claims 5 and 9 as amended herein clarify that rotigotine is present in the composition in a concentration sufficient to provide a therapeutically effective rotigotine flux for treatment of Parkinson's disease. Sufficient teaching is present in the specification to enable one of skill in the art, without undue experimentation, to determine lower and upper limits of suitable concentrations for particular situations.

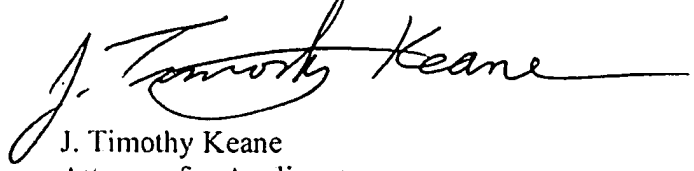
Again, although no rejection is made on this ground, Applicant responds to the comment in the Action (p. 3) implying that Claim 9 is allegedly "not commensurate in scope with the claimed invention" because it allegedly contemplates "any chloride salt". By amendment herein, the chloride salt selected has to be "pharmaceutically acceptable". Sufficient teaching is present in the specification to enable one of skill in the art, without undue experimentation, to replace the particular chloride salts exemplified with other pharmaceutically acceptable chloride salts.

4. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated or rendered moot herein. Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.

Respectfully submitted,

HARNESS, DICKEY & PIERCE, P.L.C.



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